Claims 1-3 and 15-16 were rejected under 35 USC § 102(b) as being anticipated by Dieter et al. This rejection is traversed for the following reasons.

Applicants acknowledge that the chemical compound of formula I is already known. However, Applicants do not agree that the demonstration of the existence of different modifications and their pharmaceutical application is implicitly contained in U.S. Pat. 5,384,330.

Different modifications of the chemical compounds of formula I were not known. The three modifications of compound I which are the subject matter of the present application were not inherent in the prior art.

Crystallizates were not obtained until 1994 during the transfer of the chemical method developed for the production of compound I, which is described in U.S. 5,384,330, from the laboratory into production, which crystallizates differ significantly according to the form and size of the crystals, and which resulted in problems in the reproducible production of physically and physicochemically homogeneous products.

It was the investigation of these different crystallizates, e.g. with X-ray diffraction methods, which led to the discovery of three modifications which were unambiguously identified in particular by their characteristic X-ray diffractograms (see Fig. 1 of the present specification). The coincidence-free X-ray reflexes (Bragg angles in 2 θ and d values in Å) are also indicated at pages 3 and 4 of the specification.

There are also different arrangements of the molecules of the compound of formula I, determined by X-ray photographic methods, in the

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elementary cells of the crystals of modifications A, B and C. These studies also show that A, B and C are very different.

Modification A crystallizes in the monoclinic space group $P2_1/n$.

Modification B crystallizes in the monoclinic space group C2/c.

Modification C crystallizes in the orthorhombic space group Pbca.

It was the discovery and identification of three modifications of compound I and the detailed investigation of their different physical and physico-chemical properties which made possible the development of methods for its isolation and the justification of possibilities of use for the production of special pharmaceutical formulations which are based on the particular special properties (physico-chemical stability range, crystal form, crystal size) of the individual modifications.

Modification A is stable below 80°C, even at elevated temperatures and air humidities, and exhibits no change in the crystalline structure upon contact with various solvents, especially also upon contact with water. This is advantageous in the production and storage of pharmaceutical forms of medicine under extreme conditions, e.g., in a tropical climate. Modification A has a granular nature of the powder which is favorable for the production of certain pharmaceutical formulations, e.g., for the production of tablets, on account of the preferred isometric shape of the crystals.

Modifications B and C are stable up to high temperatures (142 and 130°C, respectively) and can therefore be used in galenic processes requiring the use of high temperatures (e.g. in fusion granulation).

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Modification C, which can be produced in fine, crystalline form, can be used with advantage for the production of dry ampoules on account of its better solubility.

Summary:

The existence of three modifications of compound I was neither known nor predictable at the time of the application for U.S. Patent 5,384,330. The modifications of the compound of formula I were recognized, identified and investigated in detail for the first time by Applicants in conjunction with the development of the present invention.

The formulation on page 1, lines 31-35 of the present application presents these novel observations and investigations.

Applicants claim novel modifications, in contrast to the morphologies of which the Examiner speaks. Modifications and morphologies have <u>different</u> meanings:

Modifications require different energies (lattice energy) for the construction of their different crystalline structures and therefore exhibit defined physico-chemical properties such as characteristic melting points and transition (inversion) points (see pages 3 to 4 of the present application). Modifications are recognized by their X-ray diffraction image (see figure 1 of the present application).

The morphology, that is, the outer form and size of the crystals, is also a function of variable surface properties and local conditions of crystallization. Thus, there are numerous examples demonstrating that the same modification can form crystals of very different form as a function of the

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conditions of crystallization. Therefore, the observation of differently formed crystals by itself does not imply the presence of different modifications.

For all of the above reasons, withdrawal of the 35 USC § 102 rejection is respectfully requested.

All objections and rejections having been addressed, the application is believed to be in condition for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

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